Remarks

Applicants respectfully request the Examiner enter and consider the Supplemental Reply which is being submitted herewith in response to the Interview conduct on March 7, 2008.

Applicants assert that the Examiner has not met her burden of establishing a *prima facie* case of obviousness for the reasons elaborated in the Amendment and Reply filed of January 15, 2008, which are reiterated and incorporated herein by reference in their entirety. Applicants also present secondary indicia that further support Applicants' assertion of nonobviousness of the invention recited in the presently-pending claims.

Reconsideration of this Application is respectfully requested.

I. Statement of Substance of Interview

Pursuant to 37 C.F.R. § 1.133, Applicants provide the following statement of Substance of the Interview. Applicants wish to thank Examiner Kim and her Supervisor Examiner O'Harra for the personal interview conducted on March 7, 2008. Attorneys for Applicants discussed the outstanding 35 U.S.C. §103(a) rejection and presented additional evidence of nonobviousness, including an exhibit detailing secondary indicia of nonobviousness for consideration by the Examiner. During the interview, the Examiner specifically requested that the exhibit and arguments be formally submitted so they can be made of record.

II. Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 30, 31, 36, 44, 45, 55-57, 67, 68, 71 and 74-76 under 35 U.S.C. §103(a), as allegedly being obvious over U.S. Patent No. 5,443,976 in view of U.S. Patent No. 4,849,352, as evidenced by Harlow and Lane (Antibodies, Harlow, E. and

Lane, D., eds., Cold Spring Harbor Laboratory Press, pp. 298-99) (1988) and Campbell (Monoclonal Antibody and Immunosensor Technology, Campbell, A., ed., Elsevier Science, pp. 288-91 (1991)). *See* OA at page 7, AA at page 2. Applicants respectfully traverse this rejection for the same reasons elaborated in the Amendment and Reply of January 15, 2008, which are reiterated and incorporated herein by reference in their entirety.

A rejection based on obviousness under 35 U.S.C. § 103(a) may be overcome by presenting evidence of "secondary indicia of nonobviousness," such as, *inter alia*, commercial success, long-felt but unsolved need/failure of others, professional approval and unexpected or superior results over the prior art. *See Graham v. John Deere Co.*, 383 U.S. 1 at 7, 148 USPQ 459 at 467 (1966). Any objective evidence of nonobviousness must be considered by the Office. *See Stratoflex Inc. V. Aeroquip Corp*, 713 F.2d 1530 at 1538 (Fed. Cir. 1983). For this evidence to be given substantial weight, there must be a nexus between the evidence and the merits of the claimed invention. *Id.* at 1539, *see also* MPEP 2145.

In this case, the Applicants present a publication by Forest Jones, entitled "What's your poison: a Mexican lab hopes its antivenoms take a bite out of hospital costs across the globe," Freedom Magazine, Inc. (2005) ("the Jones article")(EXHIBIT A). The Jones article provides persuasive evidence of nonobviousness of the claimed invention, such as: long-felt and unsolved need for a safe, effective scorpion antivenom; commercial success of the claimed invention; unexpected and superior results over the prior art; and professional approval of the claimed invention by others of skill in the art.

Long-Felt Need / Failure of Others

The presently-claimed $F(ab')_2$ antibody fragment scorpion venom was not obvious at the time of filing because it satisfied a long-felt and unsolved need for a safe and effective

scorpion antivenom. Evidence that a claimed invention satisfied a long-felt but unsolved need has been held to be objective evidence that the invention is not obvious by the Supreme Court. *See Graham v. John Deere Co.*, 383 U.S. 1, 7, 148 USPQ 459, 467 (1966). The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been recognized by those skilled in the art. *Markman v. Lehman*, 987 F. Supp. 25, 43 (D. D.C. 1997) (citing *Huang*, 100 F.3d 135, 139 (n.5)), aff'd, 178 F.3d 1306 (Fed. Cir. 1998) (without opinion); *In re Gershon*, 372 F.2d 535, 539 (C.C.P.A. 1967). Second, satisfaction of the long-felt need must be part of the claimed invention, have reached a superior result to prior solutions, and the invention must in fact satisfy the long-felt need. *See Sjolund v. Musland*, 847 F.2d 1573, 1582 (Fed. Cir. 1988), *see also In re Cavanagh*, 436 F.2d 491 (C.C.P.A. 1971). Third, the length of time of the need may also be considered. *See Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996).

1. The long-felt need for a scorpion antivenom was recognized by those skilled in the art

In this case, the need for a safe, effective scorpion antivenom has been acknowledged by both scientists in the field of antivenom research as well as health officials. *See* the Jones article, paragraph 7. More specifically, in Mexico, there are about 250,000 scorpion sting victims per year, with about 800 associated deaths. *See* the Jones article, paragraph 2. In the United States, the number is about 10,000 sting victims annually. *Id.* at paragraph 2. Deaths associated with scorpion stings in the U.S. and Mexico are often due to sepsis caused by impure antivenoms and other inferior treatments. *See* the Jones article, paragraphs 2 and 4.

Unfortunately, currently there is no commercially available scorpion antivenom in the United States.

According to the Jones article, one commercial embodiment of the claimed antivenom composition, called ALACRAMYN®, is only authorized for us in Arizona, but is limited to emergency situations. *See* the Jones article, paragraph 3. Additionally, "[f]or years , Arizona hospitals have relied on homegrown antivenom that is inferior to ALACRAMYN®," and even that inferior product will soon be unavailable, as its manufacturer has ceased production. *See* the Jones article, paragraph 7.

2. The claimed F(ab')$_2$ antibody composition is superior when compared to prior antivenoms

The claimed F(ab')$_2$ antibody fragment composition satisfies a long-felt need for a scorpion antivenom, and is also superior to previously available treatments because there have been no side effects associated with the claimed composition. *See* the Jones article, paragraph 10. Toxic shock and sepsis caused by impurities in previously available antivenoms often necessitate an overnight hospital stay to monitor side effects, which significantly increases the cost of treatment per victim. Such a stay normally lasts 24 hours and can cost up to $ 8000. *See* the Jones article, paragraph 4. In contrast, the use of the presently-claimed composition has not resulted in any deaths or serious side effects, and patients can often leave the hospital within 1 hour of treatment, which drastically reduces costs. *See* the Jones article, paragraphs 2 and 4. Thus, the claimed F(ab')$_2$ antibody fragment composition is superior to previously available antivenoms and treatments because it is cheaper, safer, faster and more effective.

3. The need for the claimed product is critical because there has never been a comparable safe and effective scorpion antivenom available

Currently, there is no commercially available antivenom against scorpion stings on the market in the United States. In 2000, the last manufacturer to produce scorpion antivenom announced that they would cease further production. At that time, there was a 5 year stockpile of scorpion antivenom available to hospitals, but even that product was inferior to the current invention. *See* the Jones article, paragraph 6. This stockpile of homegrown antivenom has since run out. As discussed above, there are about 10,000 scorpion-sting victims per year in the United States, evidencing the need for a scorpion antivenom. This need has also been acknowledged by public health officials in the United States. *See* the Jones article, paragraphs 5 and 7. Although ALACRAMYN® is not yet commercially available in the United States, it is currently undergoing clinical trials. *See* the Jones article, paragraph 8. Until the product gains full FDA approval, a special exception has been granted to the state of Arizona to use the ALACRAMYN® product on emergency basis. *See* the Jones article, paragraph 3. Thus, there has always been a need for a safe, effective scorpion antivenom and that need has been exacerbated by the removal of even inferior products from the market.

Unexpected Results

A *prima facie* case of obviousness can be rebutted by showing "unexpected results." To show unexpected results, the claimed invention must possess a superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. *See In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art. *See In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991). An

examination of unexpected results is a factual inquiry. However, whether the evidence presented suffices to rebut a *prima facie* case of obviousness is part of the ultimate conclusion of obviousness and is therefore a question of law. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

In this case, Applicants have shown that the claimed $F(ab')_2$ antibody fragment composition is far superior to any previously available treatment, in part due to its unexpected ability to neutralize toxin from a scorpion belonging to a different genus than *Centruroides* (antibodies to *Centruroides* were effective in neutralizing the toxins of a variety of scorpions in the *Buthidae* family). *See* Inventor Declaration, paragraph 24, previously provided with the Amendment and Reply of June 15, 2007. A person of ordinary skill in the art at the time of filing would not have expected $F(ab')_2$ antibody fragments raised against toxin from scorpions in the genus *Centruroides* to be effective for neutralizing venom from scorpions of another genus in the *Buthidae* family. Thus, the claimed antivenom composition possess unexpected and superior results over the prior art.

Additionally, the reduced risk of side effects with the claimed composition makes this an attractive drug for use in rural settings because it will not require specialized equipment or a hospital stay. *See* the Jones article, paragraph 10. As discussed above, the claimed composition is safer, more effective and less expensive and therefore superior to previously available antivenom.

Commercial Success

Applicant may rebut a *prima facie* case of obviousness by showing commercial success. Applicant bears the burden of showing that the commercial success is in fact attributable to the claimed invention rather than to other, unrelated factors such as advertising

or unclaimed features of the product. *See Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994); see also *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) For commercial success, "prima facie evidence of [a] nexus is established if there was commercial success and if the invention disclosed in the patent was that which was commercially successful." *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991). Evidence that is suggestive of commercial success includes a showing there has been a significant growth in the market for the commercial embodiment or a showing that the sales of the commercial embodiment have replaced the sales of other products. *See Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir.1983).

Each of the presently-pending claims 30, 36, 44-45, 67 and 76-93 is directed to a composition comprising polyclonal $F(ab')_2$ antibody fragments substantially free of albumin and whole antibodies and substantially free of pyrogens, wherein the $F(ab')_2$ antibody fragments bind to a purified molecule or mixture of antigenic molecules found in the venom of scorpions of the genus *Centruroides*. Thus, the relevant market for the composition recited in the presently-pending claims is scorpion antivenoms. There are currently no FDA approved scorpion antivenoms on the market in the United States, except for ALACRAMYN® which is limited to emergency use in Arizona. *See* the Jones article, paragraph 2. Thus, even with its limited distribution, the presently-claimed composition possesses a major share of the U.S. market (arguably the entire market). Upon FDA approval, United States revenues from ALACRAMYN® sales are likely to increase significantly, further supporting a finding of commercial success. Finally, as discussed in the Jones article, the Applicants plan to expand sales of ALACRAMYN® to other countries where there is a need for scorpion antivenom, such

as Central and South America, Africa, Asia and wherever venomous scorpions are a problem. *See* the Jones article, paragraph 9.

Commercial Acquiescence Through Licensing

Applicants may also rebut a *prima facie* case of obviousness by establishing that other parties in the field consider the claimed invention nonobvious, generally by showing that one of the Applicants competitors entered into a licensing agreement that includes the asserted patent. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983).

Bioclon, the manufacturer of ALACRAMYN®, has teamed up with Rare Disease Therapeutics, a United States based company, to exclusively market ALACRAMYN® products in the United States and Canada. *See* the Jones article, paragraph 12. In addition, Bioclon has entered into a cooperation agreement with Rare Disease Therapeutics to develop other antivenoms for the United States market. *See* the Jones article, 12th paragraph. Thus, Applicants' licensing agreement regarding the presently-claimed composition is further evidence of non-obviousness. *See Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because it would not have been obvious to make composition comprising $F(ab')_2$ antibody fragments against a mixture of venoms comprising the species *Centruroides limpidus*, in light of the cited references for the same reasons elaborated in the Amendment and Reply of January 15, 2008, which are reiterated and incorporated herein by reference in their entirety. In addition, Applicants submit that they have presented compelling evidence of

secondary indicia that support a finding of nonobviousness. Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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What's your poison: a Mexican lab hopes its anti-venoms take a bite out of hospital costs across the globe

Forrest Jones

Alfredo Chavez Haro, an emergency room doctor in southern central Mexico, remembers well the six-year-old child who came into his Bed Cross emergency room. Bitten by a scorpion--just one of 230,000 victims he's seen in three decades treating every manner of calamity in his home state of Guanajuato--the child was losing control of his lungs and his throat had begun to shut. "He knew he was in the jaws of death before he should have had even a notion of what death is," Chavez says.

Scorpion stings can be fatal especially for children (this patient survived), who account for most of the country's scorpion-related fatalities. Even if the victim survives, the ordeal is traumatic. Yet deaths from such stings could become a thing of the past. A Mexican pharmaceutical company, Bioclon, has invented a drug that has cut yearly scorpion-related deaths to 100 from 800. Of the 250,000 people stung every year in Mexico, those who receive the drug--known as Alacramyn--are in and out of a hospital in an hour.

Bioclon now wants to take the anti-venom to the United States, where it is undergoing clinical studies to be approved by the Food and Drug Administration (FDA) for regular distribution. In Arizona, the drug is already authorized for use in emergencies. But public-health officials say they need it now.

The new drug, developed at Mexico's National Autonomous University (UNAM), cost just US$37, down from more than $350. "We haven't had a death or serious side effects" using Alacramyn, Chavez says. U.S. healthcare facilities rarely have to deal with life-threatening scorpion bites since many hospitals have pediatric intensive-care units, says Leslie Boyer, medical director at the Arizona Poison and Drug Information Center at the University of Arizona. However, a stay in such a facility to treat a sting normally lasts 24 hours and costs run as high as $8,000 to care for a victim. Alacramyn can cut that cost to a fraction, says Boyer.

"We are actually relying on the charity of a private Mexican organization to save the lives of rural Arizona children who would not have access to this care;' says Boyer, who stumbled across Bioclon by accident a few years ago when accompanying National Geographic magazine reporters working on a story on venomous creatures in Mexico.

While on the road, Boyer came across a lab where UNAM researchers were testing Alacramyn. Interested, Boyer withdrew a scorpion from her bag and a lab scientist used it on a test animal. The animal went from near death to recovery in about 10 minutes once it received Alacramyn, says Boyer.

For years, Arizona hospitals have relied on homegrown anti-venom that is inferior to Alacramyn. Then the manufacturer of that drug announced in 2000 it would cease production. A five-year supply is running out, and Boyer and other healthcare officials there want Alacramyn distributed as soon as possible. "I couldn't stand the thought of saying 'Sorry, we know of something good 200 miles south of the border but you can't have any'," Boyer says.

Bioclon researchers are eager to repeat their results in the United States and hope the U.S. government greenlights distribution soon. "We calculate we will finish [clinical studies] this year and present the results to the FDA and get the final biological license application, which is the last stage;' says Jorge Paniagua, head of research at Biodon, which also has begun testing antibodies to be administered to people bitten by snakes and spiders. Tests on those drugs should begin soon. "I think we are going to begin clinical studies this year," says Paniagua.

Mexico always will be Bioclon's largest market due to the sheer number of victims, but the company expects to export to Central and South America as well as Africa and Asia, wherever venomous insects and reptiles are a big problem. In the United States, only about 10,000 people suffer scorpion stings, and fatalities are very few and far between. No anti-venoms exist on the market in part because pharmaceutical companies must spend billions to bring new drugs to market. For a large drug company, the return on an investment for manufacturing and marketing anti-venoms just isn't there for a scorpion anti-venom.

Side effects. Part of what makes the drug so attractive is its ability to treat a patient with a very low risk of side effects, says Lourival Possani, head of UNAM's biotechnology institute. The drug is made by injecting venom into a horse and later extracting the antibodies from the horse's blood. UNAM scientists say they have successfully isolated only those molecules needed to fight off the poisons. Doing so lowers the risks of side effects, like toxic shock Today, UNAM is researching ways to derive anti-venoms from human blood that would eliminate problems associated from using horse blood. "People don't believe that, in a third-world country, you can do things good enough to compete in a first-world country," Possani says.

In the United States, one pharmaceutical company is ready to make emerging-country drug discoveries more available. Rare Disease Therapeutics produces pharmaceuticals and medical supplies targeted to smaller groups of consumers. Such products, known as "orphan drugs" in the industry, are designed to help the needs of people that larger drug companies would otherwise overlook due to financial considerations.

In 2001, Rare and Bioclon teamed up to bring Alacramyn into the United States, where a dull-yellow scorpion that grows up to 20 centimeters, known as the bark scorpion, poses a threat to children in the southwestern United States. The drug will be marketed under the name Anascorp in the United States. "We're basically developing that anti-venom for the state of Arizona;' says Rare Disease Therapeutics President Milton Ellis. The bark scorpion is the first creepy-crawly on its hit list. The company wants to take new Bioclon products to market in the United States, including ones designed to treat all types of rattlesnake bites as well as black widow spider bites. Rare and Bioclon are also considering making an anti-venom to treat bites from coral snakes in Florida.

Pharmaceuticals giant Merck already manufactures a drug to treat black widow bites, although that company no longer wants to produce it and is coordinating its market exit with Rare Disease Therapeutics to fill the gap, Ellis says. Once approved, Rare will distribute the Mexican anti-venoms across the United States and in Canada. One short-term obstacle, however, is having enough venom in the first place: Snakes, scorpions and spiders must be "milked" regularly to create a supply of anti-venom. "The critters have to cooperate," Ellis says.

FORREST JONES * MEXICO CITY

ONCE BITTEN

While scorpions sting thousands a year, high treatment costs can fall with new drugs.

	Number of people stung a year:	Average cost per treatment without Alacramyn:
Mexico	250,000	US $350
United States	10,000	US $6,000-US $8,000(E)

E = Estimate

SOURCE: UNAM, University of Arizona